UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Note to Reader
September 9, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply, EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, if unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues

available in the information in this docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack Housenger, Acting Director
Special Review and Reregistration
Division

DATE: September 18, 1997

MEMORANDUM

SUBJECT: **FENAMIPHOS - *FQPA REQUIREMENT* -** Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland
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THROUGH: K. Clark Swentzel
Chairman, Hazard Identification Assessment Review Committee
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TO: Karen Whitby
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PC Code: 100601

BACKGROUND: On September 2, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Fenamiphos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Fenamiphos as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document. The Committee's decisions are summarized below.

CC: Rick Whiting, Science Analysis Branch
Caswell File
LAN storage

A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Fenamiphos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Fenamiphos as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document.

B. RESULTS: Evaluation of the toxicology data base indicated the following:

1. Neurotoxicity

In an acute delayed neurotoxicity study, no clinical signs of neurotoxicity or neuropathology were seen in hens following single oral doses of Fenamiphos at doses up to and including 10 mg/kg. The Committee noted that this study did not assess the potential of Fenamiphos to inhibit neurotoxic esterase (NTE) in hens (HED Doc. No. 001308).

No treatment-related pathological lesions were seen in the central or peripheral nervous systems in an acute neurotoxicity study in Wistar rats following single oral doses at 0, 0.4, 1.6 or 2.4 mg/kg/day or in the subchronic neurotoxicity study in Fisher 344 rats following dietary administration at dose levels of 0.08, 0.8 or 3.98 mg/kg/day for 90-days. In the acute study, the LOEL was 0.4 mg/kg/day based on plasma and red blood cell (RBC) ChE inhibition (ChEI); a NOEL was not established. In the subchronic study, the NOEL was 0.08 mg/kg/day and the LOEL was 3.98 mg/kg/day based on plasma and RBC ChEI (MRID Nos. 44041501 and 44051401).

2. Developmental Toxicity

The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity to young rats or rabbits following pre-or postnatal exposure to Fenamiphos and comparable NOELs were established for adults and offspring.

In a developmental toxicity study with CD rats, pregnant animals were given oral doses of Fenamiphos at 0, 0.25, 0.85 or 3.0 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 0.85 mg/kg/day and the LOEL was 3.0 mg/kg/day based on increased mortality, reduction in body weight gain and food consumption, cholinergic signs and plasma and RBC ChEI. For developmental toxicity, the NOEL was 3.0 mg/kg/day (HDT); a LOEL was not established (MRID No. 41225401).

In a developmental toxicity study, artificially pregnant Chinchilla rabbits received oral doses of Fenamiphos at 0, 0.1, 0.5 or 2.5 mg/kg/day during gestation days 6 through 18. For maternal toxicity the NOEL was 0.5 mg/kg/day and the LOEL was 2.5 mg/kg/day based on cholinergic signs. For developmental toxicity, the NOEL was 2.5 mg/kg/day (HDT); a LOEL was not established (MRID No. 40347602).

3. Reproductive Toxicity

In a 2-generation reproduction study, when administered in the diet at 0, 2.5, 10 or 30 ppm (0, 0.17, 0.64 or 2.8 mg/kg/day for males and 0, 0.2, 0.73 or 3.2 mg/kg/day for females) to Sprague-Dawley rats, no increased sensitivity to pups over the adults was seen. For parental systemic toxicity, the NOEL was 0.17 mg/kg/day for males and <0.2 mg/kg/day for females. The LOEL was 0.64 mg/kg/day for males and 0.2 mg/kg/day for females. In both sexes, the LOELs were based on inhibition of plasma and RBC cholinesterase activity. For toxicity to the offspring and for reproductive toxicity, the NOELs were 3.2 mg/kg/day (HDT); LOELs were not established (MRID Nos.41908901 and 42491701).

In a 3-generation reproduction study, when administered in the diet at 0, 3, 10 or 30 ppm (0, 0.15, 0.5 or 1.5 mg/kg/day, respectively) to rats, no increased sensitivity to pups over the adults was seen. For parental toxicity, the NOEL was 0.5 mg/kg/day and the LOEL was 1.5 mg/kg/day based on reduced body weight gain in F1 males. For reproductive and offspring toxicity, the NOEL was 1.5 mg/kg/day (HDT); a LOEL was not established (MRID No.00037979).

4. Developmental Neurotoxicity

There are sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to Fenamiphos. These include acceptable developmental toxicity studies in rats and rabbits as well as 2-generation and 3-generation reproduction studies in rats. In addition, no treatment-related neuropathology was seen in studies conducted in hens or rats (acute and subchronic). Therefore, based upon a weight-of-the-evidence consideration of the data base, the Committee determined that a developmental toxicity study in rats is not required

5. Reference Dose

A Reference Dose (RfD) of 0.0001 mg/kg/day was derived from the NOEL of 0.01 mg/kg/day and an Uncertainty Factor (UF) of 100. The NOEL was based on plasma ChEI observed at 0.3 mg/kg/day in a 1-year feeding study in dogs. The UF of 100 included a 10 to account for intra-species and a 10 for inter-species variations.

6. Data Gaps

None

C. CONCLUSIONS

The Committee's conclusions on the Uncertainty Factors for acute and chronic dietary risk assessments are as follows:

1. Acute Dietary Risk Assessment

The endpoint selected for acute dietary risk assessment is based on inhibition of plasma (males and females) and red blood cell (males) cholinesterase activity at 0.37 mg/kg/day (LOEL) in an acute neurotoxicity study with rats. A NOEL was not established in this study. Since the dose identified is a LOEL, an additional UF of 3 was recommended.

Therefore, for acute dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity to infants and children (as required by FQPA) **should be reduced by 3-fold for a total UF of 300** (10 for inter-species variability x 10 for intra-species variability x 3 for lack of a NOEL). Consequently, **A MOE of 300 is required** to ensure protection of this population from exposure to Fenamiphos for the following reasons:

(I) The endpoint identified was cholinesterase inhibition in adult rats.

(ii) There was no evidence of maternal or developmental toxicity attributable to a an acute (single dose) *in utero* exposure of Fenamiphos in developmental toxicity studies.

(iii) An additional UF of 3 was applied to account for the lack of a NOEL in the critical study.

2. Chronic Dietary Risk Assessment

The endpoint selected for chronic dietary risk assessment is based on plasma ChEI observed at 0.3 mg/kg/day (LOEL) in a 1-year feeding study in dogs. The NOEL was 0.01 mg/kg/day. An UF of 100 was applied to the NOEL; 10 to account for intra-species and a 10 for inter-species variations. Thus a RfD of 0.0001 mg/kg/day was derived.

For chronic dietary risk assessments, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be removed.** The present **UF of 100 is adequate** to ensure the protection of this population from exposure to Fenamiphos. **Thus the RfD remains at 0.0001 mg/kg/day.** An UF of 100 is adequate since there was no indication of increased sensitivity to young animals following pre-and/or post-natal exposure to Fenamiphos as shown below:.

(I) Developmental toxicity studies showed no increased sensitivity to fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A 2-generation and a 3-generation reproduction toxicity studies in rats showed no increased sensitivity to pups as compared to adults.